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## CLINICAL RESEARCH

# Left atrial radiofrequency ablation during mitral valve surgery: a prospective randomized multicentre study (SAFIR)

Ablation de l'oreillette gauche par application de courant de radiofréquence au décours d'une chirurgie valvulaire mitrale : une étude prospective randomisée (Safir)

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## KEYWORDS

Atrial fibrillation;  
Mitral valve disease;

## Summary

**Background.** — Randomized studies evaluating left atrial radiofrequency ablation (RFA) in patients with persistent atrial fibrillation undergoing mitral valve surgery are scarce and monocentric.

**Abbreviations:** AF, atrial fibrillation; RFA, radiofrequency ablation; SAFIR, Surgery for atrial fibrillation trial.

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## Radiofrequency ablation

**Aim.** — To evaluate the efficacy of left atrial RFA concomitant with mitral valve surgery to restore and maintain sinus rhythm.

**Methods.** — The SAFIR is a multicentre, double-blinded, centrally randomized study involving four university hospitals. Between December 2002 and September 2005, 43 patients with mitral valve disease and long-standing, persistent atrial fibrillation (duration > 6 months) were included. We compared valvular surgery alone ( $n=22$ ) or with left atrial RFA ( $n=21$ ). The main endpoint was sinus rhythm at 12 months without recurrence of arrhythmia during follow-up. Secondary endpoints were surgical adverse events, atrial fibrillation relapses, stroke and echocardiographic measurements after three and 12 months' follow-up. Analyses of the efficacy criteria were performed on an intention-to-treat basis.

**Results.** — The primary endpoint occurred significantly more often in the RFA group than in the control group (respectively, 12/21 patients [57%] vs 1/22 patients [4%];  $p=0.004$ ). There were more patients with sinus rhythm in the RFA group than in the control group at discharge (72.7% vs 4.8%;  $p<0.005$ ), 3-month follow-up (85.7% vs 23.8%;  $p<0.01$ ) and 12-month follow-up (95.2% vs 33.3%;  $p<0.005$ ). The patients in the RFA group had similar rates of postoperative complications and stroke during follow-up as those in the control group.

**Conclusions.** — This multicentre study suggests that left atrial RFA is effective and safe in patients with chronic atrial fibrillation and mitral valve disease.

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## MOTS CLÉS

Fibrillation atriale ;  
Valvulopathie mitrale ;  
Ablation par courant  
de radiofréquence

## Résumé

**Justification.** — Les études randomisées évaluant l'ablation de la fibrillation atriale par application de courant de radiofréquence au décours d'une chirurgie mitrale sont rares et monocentriques.

**Objectifs.** — Évaluer l'efficacité de l'ablation de la fibrillation atriale compliquant une pathologie valvulaire mitrale pour obtenir le retour et le maintien du rythme sinusal.

**Méthodes.** — L'étude Safir est un essai multicentrique réalisé en double insu avec randomisation centralisée impliquant quatre hôpitaux universitaires. Entre décembre 2002 et septembre 2005, 43 patients avec maladie valvulaire mitrale et fibrillation atriale persistante (durée supérieure à six mois) ont été inclus. Nous avons comparé la chirurgie valvulaire isolée ( $n=22$ ) à la chirurgie vasculaire associée à un geste d'ablation de l'oreillette gauche ( $n=21$ ). Le critère de jugement principal était la présence d'un rythme sinusal à 12 mois sans récurrence de l'arythmie pendant le suivi. Les événements indésirables postchirurgicaux, les rechutes de fibrillation atriale, les accidents vasculaires cérébraux et les mesures échocardiographiques à trois mois et 12 mois ont été colligés. L'analyse de l'efficacité a été réalisée en intention de traiter.

**Résultats.** — Douze mois après l'intervention, 57% des patients dans le groupe radiofréquence étaient en rythme sinusal, (12/21) contre 4% (1/22) dans le groupe témoin. Après 12 mois de suivi, la proportion de patients en rythme sinusal était significativement plus élevée dans le groupe radiofréquence que dans le groupe témoin 12/21 patients (57% versus 1/22 patients, 4%;  $p=0,004$ ). Il y avait, de façon statistiquement significative, plus de patients en rythme sinusal à la sortie de l'hôpital dans le groupe radiofréquence par rapport au groupe témoin (72,7% versus 4,8%;  $p<0,005$ ). La même différence en faveur du traitement par application de courant de radiofréquence était observée à trois mois (85,7% versus 23,8%;  $p<0,001$ ) et à 12 mois de suivi (95,2% versus 33,3%;  $p<0,005$ ). Les patients du groupe traitement par radiofréquence avaient des taux de complication postopératoire et d'accident vasculaire cérébral pendant le suivi identique à ceux du groupe témoin.

**Conclusion.** — Cette étude multicentrique suggère que l'ablation de la fibrillation atriale au décours d'une chirurgie valvulaire mitrale est efficace chez les patients avec fibrillation atriale persistante.

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## Background

Approximately 50% of patients with mitral valve disease that requires surgery present with AF [1–5]. Because over 70% of these patients continue to have arrhythmia after corrective surgery [1,4], antiarrhythmic surgical treatments have been developed. Since 1987, antiarrhythmic surgery for AF has

essentially been based on a method of compartmentalization of the left and right atria by a cut-and-sew procedure called 'Maze', which was developed by Cox et al. [6,7]. This reference technique is complex and requires more than 45 minutes of extracorporeal circulation; consequently, it has only been used successfully by a few highly specialized surgical teams. The success of catheter ablation has paved

the way for newer surgical approaches using simpler compartment surgery [8]. On the other hand, the antiarrhythmic efficacy of a Maze procedure with a less extensive muscle cut has been suggested by Cox et al. [6]. Sueda et al. were the first to perform a left atrial lesion set for AF concomitant to mitral valve surgery [9]. These investigators obtained an AF-free rate of 78% at 12 months. The limited segmentation pattern was based on mapping, which demonstrated shorter cycle length in the left atria compared with the right atria. One randomized study compared left versus biatrial cut-and-sew techniques [10], but found no difference between the two strategies, with an AF-free rate of 70% at one year in the left atrial lesion set arm.

Deneke et al. [11] compared left versus biatrial RFA as an antiarrhythmia intervention, and found no significant difference between the two procedures. In two non-randomized, single-centre studies [12,13], the success rate – defined as the persistence of sinus rhythm at one year – reached 70% with the left atrial ablation only approach. With the same lesion set, one randomized, single-centre study suggested that sinus rhythm can be achieved at one year in 44% of the patients treated with RFA [14]. In the era of evidence-based medicine, there is a lack of multicentre studies for the precise quantification of the risk-benefit ratio of left atrial RFA associated with mitral valve surgery. In such a setting, the fact that a cure for AF has not been proven to improve the long-term prognosis [15] reinforces the need for a solid validation methodology. Recently, a consensus statement on surgical ablation of AF reminded us that ‘multicentre clinical trials are needed to better define the relative safety and efficacy of various surgical tools and techniques’ [16]. The aim of the SAFIR, a multicentre, double-blinded, centrally randomized study, was to evaluate the efficacy of left atrial RFA concomitant with mitral valve surgery to promote sinus rhythm.

## Methods

### Patient population

This trial was conducted according to French and European Good Clinical Practices, and in keeping with the principles of the Declaration of Helsinki in its current version, and with French Law No. 88-1138 of 20 December 1988, modified on 25 July 1994. This protocol was approved by the *Comité consultatif de protection des personnes se prêtant à des recherches biomédicales* Lyon A Committee on 17th May 2001.

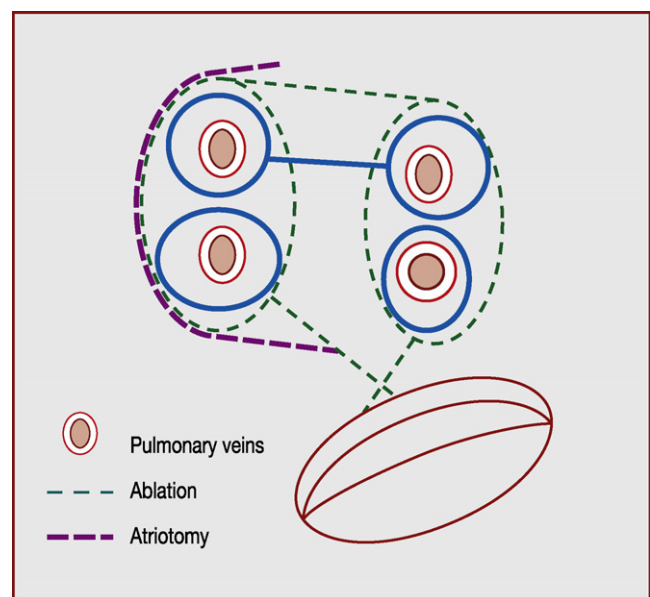
This double-blind, multicentre study was performed at four university hospitals between August 2002 and September 2005. At each of the four centres, patients aged equal or over 18 years who were admitted for mitral valve disease requiring surgery that was associated with persistent AF evolving for more than six months were eligible. Patients with left ventricular ejection fraction less than 35% and left atrial transverse diameter greater than 60mm were excluded. Immediate postoperative treatment and prescription medication upon discharge were left to the discretion of the physician in charge of the patient. Anticoagulant treatment was maintained for at least three months after surgery.

### Surgical procedures

The RFA group included mitral valve surgery via the Waterstone groove associated with isolation of the pulmonary veins one by one or two by two. This procedure was completed by an RFA line on the roof of the left auricle and a line joining the inferior borders of the right or left inferior radiofrequency lesions to the mitral ring in its posteromedian region (Fig. 1). Isolation of the left appendage was left to the discretion of the surgeon. Radiofrequency lesions were made with a temperature-controlled 8 F/8mm catheter (EP Technologies, Boston Scientific Corp, San Jose, CA, USA), as described previously [17].

### Follow-up

After centralized randomization, all patients were followed in parallel for 12 months, with three hospital consultations (at discharge, and again at three and 12 months). RFA was considered successful if sinus rhythm was maintained at 12 months with no symptomatic or documented episodes of AF on repeated Holter monitoring during the entire follow-up period. At the last follow-up visit, all the patients had Holter monitoring. The secondary endpoints included the following: adverse surgical events, stroke, AF recurrence (defined as a new episode of symptomatic AF or AF confirmed by electrocardiogram), death by any cause and severe, undesirable events other than death. Upon discharge, the physician in charge of blinded follow-up examined the patient and collected data related to the endpoint criteria. Consultations at three and 12 months were performed on an outpatient basis. Validation of the endpoint criteria was carried out by a critical-event validation panel made up of three cardiologists who did not otherwise participate in the study.



**Figure 1.** Location of the left atrial lesion sets. Isolation of the left appendage was left to the discretion of the surgeon.

## Statistical analysis

According to the data in the literature when the study was designed [1,4], approximately 70% of patients with AF of valvular origin for more than one year keep this arrhythmia after isolated valve replacement versus only 20% of cases with associated antiarrhythmic surgery [1,4]. With an alpha risk set at 5% and a beta risk at 10%, the number of patients required was estimated to be at least 23 patients per group. To account for patients lost to follow-up, an enrolment of 30 patients per group was considered sufficient. Enrolment was slower than anticipated and was therefore extended to two years, but ceased in September 2005 due to lack of funding.

Analyses of the efficacy criteria were performed on an intention-to-treat basis. Continuous data are expressed as mean  $\pm$  standard deviation. All statistical tests were bilateral with a significance threshold of 0.05. Group comparisons were performed with the Chi<sup>2</sup> test or Fisher's exact test and Student's *t*-test.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

### Study population

Forty-three patients from four centres were randomized: 21 to the RFA group and 22 to the control group. Demographic data are shown in Table 1. Only weight and height were significantly lower in the RFA group. Surgical data are presented in Table 2. The proportion of patients treated for mitral valve replacement was higher in the control group than in the RFA group (80.9% vs 45.4%, respectively;  $p = 0.03$  [0.03]). The mean aortic cross-clamp duration was similar in the RFA group and in the control group ( $74 \pm 21$  min vs  $93 \pm 32$  min [74 min vs 93 min, respectively]). The mean duration of initial hospitalization was similar in both groups (16 days).

### Follow-up

After one year of follow-up, the primary endpoint occurred significantly more frequently in the RFA group than in the control group (12/21 patients [57%] vs 1/22 patients [4%], respectively;  $p = 0.004$ ). This difference favouring RFA was

**Table 1** Demographic, clinical and echocardiographic data.

	Valve surgery alone (n = 22)	Radiofrequency ablation (n = 21)	p
Age (years)	66.31 $\pm$ 9.7	69.1 $\pm$ 6.2	0.27
Men	11 (50.0)	5 (23.8)	0.14
Weight (kg)	73.6 $\pm$ 14.2	62.4 $\pm$ 9.8	0.005
Height (cm)	167.5 $\pm$ 10.7	161.7 $\pm$ 7.7	0.05
Mean atrial fibrillation duration (months)	89.2	161	0.12
Mitral regurgitation	14 (63.6)	12 (57.1)	0.75
Mitral stenosis	5 (22.7)	4 (19.1)	1
History of atrial flutter	2 (9.1)	3 (14.3)	0.66
Previous myocardial infarction	2 (10)	3 (13 [ ])	1
History of stroke	2 (13)	0 (0)	0.22
Hypertension	6 (50)	8 (66)	0.4
Heart failure	[16] (75.0)	[13] (63.6)	1
LVEF (%)	61.3 $\pm$ 9.45	59.8 $\pm$ 8.5	0.59
LVEDD (mm)	54.3 $\pm$ 8.3	51.86 $\pm$ 7.89	0.35
Left ventricular hypertrophy	19 (86.4)	18 (85.7)	1
Left atrial diameter (mm)	52.6 $\pm$ 11	54.63 $\pm$ 10.9	0.58

Values are number (%) or mean  $\pm$  standard deviation. Not all patients were assessed for each categorical characteristic. LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction.

**Table 2** Surgical data.

	Valve surgery alone (n = 22)	Radiofrequency ablation (n = 21)	p
Mitral valve repair	13 (59.9)	4 (19)	0.01
Mitral valve replacement	17 (80.9)	10 (45.5)	0.03
Tricuspid annuloplasty	6 (27.3)	1 (4.8)	0.1
Aortic valve replacement	3 (13.6)	3 (14.2)	1
Aortic clamp time (min)	74 $\pm$ 19	93 $\pm$ 32	0.4
Mean hospital stay (days)	16	16	0.5

Values are number (%) or mean  $\pm$  standard deviation.

**Table 3** Sinus rhythm at each consultation.

	Valve surgery alone ( <i>n</i> = 22)	Radiofrequency ablation ( <i>n</i> = 21)	<i>p</i>
Discharge	1 (4.76)	16 (72.73)	0.005
At 3 months	5 (23.81)	18 (85.71)	0.0126
At 12 months	7 (33.33)	20 (95.24)	0.005
Values are number (%).			

also present after three and 12 months (Table 3). At 12 months, the numbers of class I, II and III antiarrhythmic prescriptions were similar in the two groups (control vs RFA: 1 vs 2, 11 vs 7 and 6 vs 7, respectively). Eighteen patients in the control group were treated with diuretics versus 13 in the RFA group ( $p = 0.14$ ). Twenty-one patients in the control group were treated with vitamin K antagonists versus 13 in the RFA group. Thirteen of 43 (30%) patients underwent electric cardioversion during follow-up (11 in the control group and two in the RFA group). No patient was lost to follow-up.

## Clinical events

There were 39 validated intercurrent events in 22 patients. Without reaching the significance threshold, the proportion of patients presenting with at least one undesirable event was higher in the control group than in the RFA group (11/22 [50%] patients vs 16/21 [76%] patients, respectively;  $p = 0.14$ ). There was one death in the RFA group. This patient, who had undergone tricuspid and mitral valve replacement, presented with postoperative cardiogenic shock rapidly followed by massive ischaemic stroke. It was necessary to implant pacemakers in five patients (three patients in the RFA group and two patients in the control group). One patient from each group underwent a second valve replacement. Four patients presented with severe postoperative haemorrhaging: one patient in the RFA group (haematoma of the psoas) and three patients in the control group (mediastinal bleeding and haemothorax). Three patients in the RFA group had strokes. One patient has postoperative left hemiplegia due to gas embolism. Another patient was readmitted seven months postoperatively after a cerebrovascular accident in the context of a prosthetic thrombosis. A second mitral valve replacement was performed. During the immediate postoperative period, one patient suffered a comitial crisis with hemiplegia that was resolved in less than six hours. In the control group, only one patient presented with a transitory cerebral ischaemic accident. One patient in each group had atrial tachycardia.

## Echocardiographic data

The size of the left atria at three months was significantly smaller in the RFA group than in the control group ( $45.90 \pm 7.46$  mm vs  $52.71 \pm 7.12$  mm, respectively;  $p = 0.01$ ). Although this difference persisted at 12 months, it was no longer significant. At the end of the trial, all 12 patients with sinus rhythm in the RFA group had an A-wave with a mean velocity of  $69 \pm 30$  mm/s. The A-wave velocity was significantly lower in nine patients in the RFA group than in 12 patients in the control group at three months

( $0.73 \pm 0.42$  vs  $1.67 \pm 0.25$  cm/s, respectively;  $p = 0.005$ ) and 12 months ( $0.69 \pm 0.30$  vs  $1.04 \pm 0.25$  cm/s, respectively;  $p = 0.04$ ). The left ventricular ejection fraction and left ventricular end-diastolic diameter measured at discharge, three months and 12 months were similar in the two groups, with a tendency toward reduction of the left ventricular end diastolic diameter in the RFA group compared with the control group ( $48.67 \pm 4.23$  mm vs  $51.19 \pm 7.30$  mm, respectively;  $p = 0.22$ ).

## Discussion

To our knowledge, this study is the first multicentre trial to confirm the efficacy of left atrial RFA associated with mitral valve surgery to maintain sinus rhythm one year postoperatively. However, because of the absence of difference in the stroke rate between the two groups, the study does not support any benefit of the ablation procedure. The overall complication rate, vascular cerebral event rate and duration of initial hospitalization did not differ in patients who received RFA compared with the control group, although the duration of extracorporeal circulation was higher in the RFA group than in the control group.

The SAFIR trial had three methodological advantages compared with studies published previously: it had a multicentre design, a centralized randomization procedure, and validated endpoint criteria and adverse events as determined by an independent panel of experts. The number of patients included was close to the number required per the protocol (23 evaluable patients per group in the final analysis). No patient was lost to follow-up. The independent funding and a complete report of adverse events also represent the study's strengths.

## Previous studies

Few studies have evaluated endocardial left atrial RFA concomitant to valve surgery [12–14,18]. The two previous randomized trials had methodological flaws that limited their interpretation [14,18]. What RFA lesions have in common in all studies is complete isolation of all the pulmonary lesions associated with at least one line drawn towards the mitral valve annulus. Deneke et al. [18] compared the outcomes of 15 patients who had a combined procedure with 15 patients who had valve surgery alone. At 12 months, 81.8% of patients with left-sided ablation were in sinus rhythm versus 21.4% in the surgery-alone group. In a study of 101 patients with mitral valve disease and permanent AF, Doukas et al. [14] reported that sinus rhythm was present after one year of follow-up in 44.4% of the patients in the mini-Maze group



versus 4.5% of the 44 patients in the control group. This previous study, like the SAFIR study, had a lower success rate than that of non-randomized investigations. Interestingly, the average efficacy of 50% correlates with the left atrial catheter ablation in patients with heart failure and chronic AF [19]. By comparison, Cox-Maze III RFA has been evaluated in one randomized study involving 70 patients with permanent AF [20]. The efficacy of this extensive ablation lesion set that yields a 79% freedom from arrhythmias is in accord with the critical mass hypothesis [21]. The debate over whether or not the left atrial appendage should be included in the lesion set is neither fuelled nor enlightened by the SAFIR study. Adverse event profile

An important issue is related to the risk–benefit equation of an additional ablation procedure in mitral valve patients. Although the adverse event rates were particularly high in the SAFIR study, they did not differ between groups. Other studies are in agreement with these results, strengthened by the fact that the duration of hospitalization was the same in the two groups with and without RFA [14]. With left atrial ablation surgery, complications such as excessive bleeding or abnormal heart rhythm requiring pacemaker implantation also appear to be less frequent than those observed with the bi-atrial Cox-Maze procedure [11].

### Atrial transport function

The quality of left atrial mechanical function is essential to reduce the risk of thromboembolic stroke. In the SAFIR trial, the antiarrhythmic RFA intervention was associated with a reduction in the size of the left atrium compared with that in the control group. This difference was maintained at 12 months, but was not significant. Interestingly, atrial contractility was lower in the control group than in the mini-Maze group. Decreased contractility has also been documented after left atrial circumferential catheter ablation [22]. The fact that muscle cut may lead to abnormal left atrial velocity was also strengthened with a surgical approach by Lønnerholm et al. [23]. Precise quantification with new imaging techniques for atrial transport function is needed to provide information on the necessity for anticoagulant therapy in patients in sinus rhythm after surgical ablation of AF.

### Study limitations

The absence of detection of asymptomatic paroxysmic AF is the main limitation of this study. However, AF recurrence in the patient population studied in this trial occurs preferentially in the persistent rather than in the paroxysmic mode. Moreover, the restrictive character of the principal endpoint adopted in the SAFIR trial (sinus rhythm at each evaluation and an absence of symptomatic AF between consultations) consolidates the efficacy results observed. The proportion of patients with mitral valve replacement was significantly higher in the control group than in the RFA group. However, because the type of mitral surgery has not been described as a prognostic factor for the recurrence of AF, it is unlikely that this characteristic influenced our results. Finally, the impact of coronary disease on the ablation procedure as suggested by Melo et al. [24] was not evaluated owing to the size and the design of the study, which precluded firm conclusions being made regarding changes attributed to this condition.

## Conclusions

The results of this multicentre study confirm that RFA limited to the left atrium during mitral surgery increases the chance of maintaining sinus rhythm at one year. Importantly, the RFA procedure was not associated with increased morbidity. The SAFIR study results suggest that improved ablation procedures should make it possible to obtain better electrical stability results.

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## Conflicts of interest

None.

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